MAIL STOP AMENDMENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	H. Lowenheim	Attorney Docket No.:	SOPH116953
Application No.:	09/622,719	Group Art Unit:	1635
Filed:	October 18, 2000	Examiner:	K.A. Lacourciere
Title:	METHOD FOR THE TREATMENT OF DISEASES OR DISORDERS OF THE INNER EAR		

RESPONSE TO OFFICE ACTION

Seattle, Washington 98101
December 29, 2004

TO THE COMMISSIONER FOR PATENTS:

In view of the arguments that follow, and the declaration of Jonathan Kil submitted herewith, applicant submits that all the pending claims are in condition for allowance.

Rejection of Claims 28, 31, and 63 Under 35 U.S.C. § 112, First Paragraph, for Alleged Lack of Adequate Written Description

The Examiner argues that the genus of mammalian $p27^{Kip1}$ antisense required to practice the claimed methods do not meet the written description provision of 35 U.S.C. § 112, first paragraph, because none of the species encompassed by the genus were described in the specification, and a sufficient number of species to represent the genus were not described in the prior art. Additionally, the Examiner argues that the genus of mammalian $p27^{Kip1}$ is broad and the species encompassed in the genus is highly variant (for example, with regard to nucleotide sequence), and therefore the structure (i.e., nucleotide sequence) of antisense molecules targeting this genus is highly variant.

As a preliminary matter, applicant respectfully notes that the Examiner does not provide any basis to support the assertion that the species encompassed by the genus of mammalian $p27^{Kip1}$ molecules is highly variant, for example with regard to nucleotide sequence. Applicant submits that, on the contrary, the art teaches that the species encompassed within the genus of mammalian nucleic acid molecules encoding $p27^{Kip1}$ proteins, have highly related sequences. For example, in the response submitted on June 9, 2004, together with the Request for Continued

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Examination, applicant provided a Clustal W Alignment of the nucleic acid sequences encoding human, mouse, and mink $p27^{Kip1}$ proteins. This alignment showed that these three nucleic acid sequences are more than 85% identical (response filed June 9, 2004, at page 7, and Attachment D). Further, as described by Polyak et al. (*Cell 78*:59-66 (1994)), which was made of record in the response dated November 4, 2003, the $p27^{Kip1}$ proteins encoded by these nucleic acid molecules are about 90% identical (Polyak et al., page 61, last line, to page 62, line 2). Thus, applicant submits that the art teaches that the species encompassed by the genus of mammalian $p27^{Kip1}$ molecules are highly conserved.

Submitted herewith, as Attachment A, is the declaration of Jonathan Kil (hereinafter referred to as the Third Kil Declaration). A copy of Jonathan Kil's *Curriculum vitae* was made of record in the response dated June 9, 2004. The Third Kil Declaration describes the results of experiments in which 14 antisense oligonucleotides (directed against mouse $p27^{Kip1}$ mRNA) were introduced into mouse NIH 3T3 cells, cultured *in vitro*, and subsequently the level of $p27^{Kip1}$ mRNA was measured.

The nucleic acid sequences of the 14 antisense oligonucleotides are set forth in Table 1, paragraph 3, of the Third Kil Declaration. As described in paragraph 3 of the Third Kil Declaration, the location of each oligonucleotide is given with reference to the sequence of the mouse $p27^{Kip1}$ cDNA (GenBank accession number U09968; reported in Polyak, K., et al, *Cell 78*: 56-66 (1994).

As described in paragraph 3 of the Third Kil Declaration, the cells were incubated in the presence of the oligonucleotide for 26 hours. Real time PCR was used to measure the amount of $p27^{Kip1}$ mRNA present in total RNA extracted from the treated cells.

Enclosed herewith as Attachment B is a graph showing the level of $p27^{Kip1}$ mRNA in the cells treated with the different oligonucleotides, compared to the control level of $p27^{Kip1}$ mRNA in cells treated with the Lipofectamine lipid delivery vehicle without oligonucleotides. As described in paragraph 4 of the Third Kil Declaration, the results shown in the graph demonstrate

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

that all of the tested oligonucleotides caused a significant reduction in the level of $p27^{Kip1}$ mRNA in the treated cells.

As can be seen from Table 1 of the Third Kil Declaration, the antisense oligonucluotides each corresponded to a different sequence within the first 445 bases of the $p27^{Kip1}$ mRNA. Thus, the results of these experiments are consistent with the view that the level of expression of a $p27^{Kip1}$ mRNA can be significantly reduced by an antisense oligonucleotide that corresponds to any sequence of at least 14 consecutive nucleotides within a $p27^{Kip1}$ mRNA. Consequently, in this case the applicant submits that the written description requirement is satisfied by the existence, in the prior art, of the nucleic acid sequence of at least one member of the highly conserved genus of mammalian $p27^{Kip1}$ mRNAs (e.g., the sequence of the mouse $p27^{Kip1}$ cDNA, set forth in the GenBank database as accession number U09968, which was reported by Polyak et al. in 1994) that can be used as a source of antisense oligonucleotide sequences.

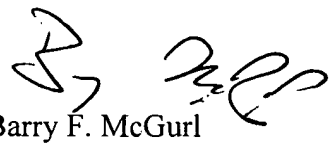
Consequently, applicant requests withdrawal of the rejection of Claims 28, 31, and 63 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the foregoing arguments, and the results of the experiments described in the Third Kil Declaration, applicant respectfully submits that all the pending claims are in condition for allowance. Reconsideration and favorable action are requested.

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS^{PLLC}



Barry F. McGurl
Registration No. 43,340
Direct Dial No. 206.695.1775

I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

Date: _____ _____ BFM:jam/tmm

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS^{PLLC}
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100